Section III (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, claim 10 has been amended to correct a typographical error and claim 23 has been added. Support for new claim 23 may be found in Example 5, as filed. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application.

In view of the finality of the October 14, 2009 Office Action and to ensure substantive consideration of this response, a Request for Continued Examination is concurrently submitted herewith, together with payment of the appertaining RCE fees (see *infra*, "CONCLUSION").

B. Objections to the Specification

In the Final Office Action mailed October 14, 2009, the examiner maintained the objections to the specification with regard to the paragraph at page 4, line 21 to page 5, line 10. All amendments requested by the examiner have been made, as set forth in Section I above. In addition, the paragraph at page 5, lines 24-26 has been amended as indicated in Section I above. These amendments had previously been submitted in the Response filed August 3, 2009, however the page number was mistakenly identified as page 4.

No new matter is added by such amendments. As amended, the sequences identified in the specification are consistent with the Revised Sequence Listing submitted August 3, 2009.

C. Rejection Under 35 U.S.C. §112, first paragraph

In the Final Office Action mailed October 14, 2009, the examiner rejected claim 10 as failing to comply with the written description requirement. The rejection is based on recitation of a "CGC" spacer in the claimed scaffold. As noted by the examiner, recitation of a "CGC" spacer was a typographical error. The examiner's attention is respectfully drawn to Section II above,

where "CGC" has been amended to "CGG." In the Final Office Action mailed October 14, 2009 the examiner suggested that "[a]mending the claim to recite 'CGG' would be remedial."

In view of the amendment of claim 10, withdrawal of the rejection is respectfully requested.

D. Priority

The examiner's conclusion that priority to Korean Patent Application 10-2004-0019010 is denied with respect to SEQ ID NO: 6 is acknowledged by Applicants.

Election of SEQ ID NO: 6 is simply a species election, made at the examiner's request. The examiner is reminded that different claims in an application may have different priority dates (*See* MPEP §201.15). To the extent that support for any subject matter within the claims is present in Korean application 10-2004-0019010, priority to the application is claimed.

E. Rejection of Claims under 35 U.S.C. §103(a)

In the Final Office Action mailed October 14, 2009, the examiner rejected claims 10, 13, 21 and 22 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,409,764 (hereinafter White et al.) in view of International Publication No. WO2005/113585A2 (hereinafter "Knopf"), Gauvreau et al., 2004, *Bioconjugate Chem.*, 15:1146-1156 (hereinafter Gauvreau et al.) and U.S. Patent No 6,316,003 B1 (hereinafter Frankel et al.). Applicants respectfully traverse the rejection.

The examiner's attention is respectfully drawn to amended claim 10 above. As amended, the claim recites a scaffold with the characteristics of: 1) immobilization of the peptide on the scaffold in an amount of 0.1-10 mg/cm^2, 2) addition of CGG spacer at the N-terminal end of the tissue growth factor-derived peptide, 3) the scaffold is an implant and the surface of the implant is modified by oxidation and nitrification to facilitate the adhesion of the active peptide to the surface. The cited combination of prior art does not disclose such a scaffold.

White et al. is cited as the primary reference with regard to the present rejection. In the discussion of White et al., the examiner alleged that "'764 teaches a bone graft material or scaffold for tissue engineering applications such as implants comprising BMP-2 immobilized on

the surface." (Final Office Action mailed October 14, 2009, p. 6.) Applicants previously established that White et al. merely teaches placing TGF-β proteins in a space within a tissue penetrable device and not immobilized on the surface of the implant, as required by Applicants' claimed invention. In Response the examiner replied:

> "[t]his has been fully considered but is not found to be persuasive. As taught by White et al. ('764) at col. 25, third paragraph, treatment iii involved pretreatment of ePTFE and PGA:TMC membranes by coating with polyethylene imine, followed by cross-linking with ethylene glycol bis[succinimidyl-succinate] (EGS) and then adding BMP-2 with sulfo-EGS to reversibly cross-link the BMP-2." (Final Office Action mailed October 14, 2009, p. 10.)

While Applicants acknowledge the examiner's citation of this portion of White et al., it is respectfully submitted that this portion does not show immobilization or cross linking on a graft described by White et al. as conducive to generation of bone or periodontal tissue *in vivo*.

The examiner's attention is respectfully drawn to col. 25, lines 5-12, where it is described that various carriers were used in a release experiment. Four types of materials were used: 1) an expanded polytetrafluoroethylene (ePTFE) membrane, 2) a membrane made from a polyglycolide:trimethylene carbonate)(PGA:TMC) block copolymer, 3) a collagen sponge and 4) a hyaluronic acid (HA) felt. At col. 25, lines 24-49 three specific treatments of the membranes are described to yield a total of ten carrier samples (ePTFE, ePTFE(i), ePTFE(ii), ePTFE(iii), PGA:TMC, PGA:TMC(i), PGA:TMC(ii), PGA:TMC(iii), collagen sponge and HA felt). At col. 27, lines 9-38 the results of the experiment are provided where it is reported that:

> "[f]or all eight membrane groups, the results were essentially identical. In excess of 93% of the rhBMP-2 loaded onto each membrane was released in the first 24 hrs. Less than 0.5% of the initial rhBMP-2 loaded was released from the membrane delivery devices over the preceding 24 hr period when sampled at three days. When a large percentage of the loaded agent is released in the initial portion of the desired release period, it is called a burst effect. In the application of the present invention, it is desirable to have sustained release of rhBMP-2 over a period of several days to achieve substantial induced bone formation in vivo. Since more than 93% of the rhBMP-2 was released in the first 24 hrs, the use of membrane delivery devices, such as those described here, would not be expected to provide rhBMP-2 (or other TGF-Beta proteins) to the host system for the several days necessary to achieve substantial bone or periodontal tissue formation. An acceptable rhBMP-2 delivery profile was not achieved using any of the membrane delivery devices tested. (Emphasis added.)

This demonstrates that for all of the membranes, **including the pretreated membranes cited by the examiner**, a burst effect was observed. It is the conclusion of White et al. that "the use of membrane delivery devices, such as those described here, would not be expected to provide

rhBMP-2 (or other TGF-Beta proteins) to the host system for the several days necessary to achieve substantial bone or periodontal tissue formation." As an alternative, White et al. show that:

> "[i]n contrast, the initial 24 hr release from the collagen sponge and the HA felt only constituted 29.3% and 33.3% of the initial loading, respectively. Even after 7 days, 2.6% and 3.0% of the initial rhBMP-2 loaded were released from the collagen sponge and HA felt, respectively, over the preceding 24 hr period. When used as carriers for rhBMP-2 (or other TGF-Beta proteins) a collagen sponge or an HA felt may be expected to exhibit a biologically acceptable delivery profile sufficient to achieve substantial bone or periodontal tissue formation in vivo." (col. 27, lines 29-38)

Accordingly, White et al. conclude that:

> "The collagen and hyaluronic acid carriers used in this study exhibited sustained release of a TGF-Beta protein (rhBMP-2) over a period of several days. Both the collagen and hyaluronic acid carriers may be expected to achieve an acceptable delivery profile conducive to generation of bone or periodontal tissue in vivo. **In contrast, the membranes impregnated with a TGF-Beta protein (rhBMP-2) were not shown to achieve an acceptable delivery profile conducive to generation of bone or periodontal tissue in vivo**." (col. 27, lines 40-49; emphasis added)

The examiner is reminded that in considering a reference for its effect on patentability, the reference is required to be considered in its entirety, including portions of teach away from the invention under consideration. Simply stated, the prior art must be considered as a whole. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); MPEP § 2141.02.

As graphically illustrated in Graph A of White et al., it is the conclusion of White et al. that space filling carriers, such as sponge and HA felt, which merely have TGF-β proteins placed in a space are superior to membrane carriers, including pretreated membranes. White et al. discourages one of skill in the art from using, "...a bone graft material or scaffold for tissue engineering applications such as implants comprising BMP-2 immobilized on the surface" (Final Office Action mailed October 14, 2009, p. 6; emphasis added), where the membrane demonstrates an undesirable burst effect.

Therefore White et al. teach away from using carriers other than space filling carriers. White et al. teach away from membranes, including pretreated membranes, which are subject to a burst effect, as carriers for TGF-β and away from demonstration that such would be conducive to generation of bone or periodontal tissue *in vivo*.

Additionally, the examiner cited Knopf as demonstrating "the exact BMP-2 fragment of SEQ ID NO: 6 at p. 20, line 4..." (Final Office Action mailed October 14, 2009, p. 7). Knopf, however, merely suggests that a chimeric TGF-β superfamily protein, which comprises a core domain from a first TGF-β superfamily member will be effective. However, one of skill in the art would not necessarily expect that the variable domain itself would be effective. The sequence at page 20, line 4 of Knopf, as cited by the examiner is simply a variable domain. There is no reasonable expectation of success in using this variable domain from Knopf in a membrane system not expected to be successful in delivering proteins to a host system.

"A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." (MPEP 2143.01)

As set forth above, White et al. teach away from using the membranes as carriers. There would have been no motivation to modify the carriers identified by White et al. as "not...expected to provide rhBMP-2 (or other TGF-β proteins) to the host system..." (White et al., col. 27, lines 23-24.) Furthermore, there is no motivation in White et al. to use BMP fragments on such membrane carriers. Additionally, there is no motivation in the combination of references to use the variable domains of Knopf on such carriers.

The examiner also cited Gauvreau et al. as "discuss[ing] the use of sulfo-SMCC to achieve cross-linking of a cysteine-containing protein to a solid substrate in order to immobilize the protein... [and] teach[ing] oxidation and nitrification to facilitate adhesion of proteins to solid supports." Frankel et al. was cited as "teach[ing] the addition of CGG to the N-terminus of a tat protein fragment that lacked a cysteine, and the use of sulfo-SMCC modified ribonuclease to achieve a cross-linking reaction." (Final Office Action mailed October 14, 2009, p. 7). The citation of Gauvreau et al. and Frenkel et al. do not remedy the deficiencies of the combination of White et al. and Knopf. The combination of references does not render obvious a scaffold for tissue engineering containing a peptide immobilized on the scaffold, a CGG spacer at the N-terminal end of the peptide, and where the scaffold is an implant and the surface of the implant is

modified by oxidation and nitrification to facilitate the adhesion of the active peptide to the surface.

Additionally, the claims of the invention recite a peptide immobilized in an amount of 0.1-10 mg/cm^2. It is the examiner's assertion that optimization of ranges is well within the skill of those in the art, in the absence of evidence of unexpected results. (Final Office Action mailed October 14, 2009, p. 7).

The examiner's attention is respectfully drawn to paragraphs [0005] and [0006] of the specification, where it is described how in the past it was believed that growth factors needed to be administered at high doses to achieve the desired therapeutic effect, in order to combat the burst effect.

Accordingly, the prior art taught away from experimentation in the range of 0.1-10 mg/cm^2. The present inventors made extensive efforts to solve the problems in the prior art, and consequently found that a bone graft material and scaffold having a surface immobilized with the active site peptides of a tissue growth factor and an extracellular matrix protein, which can achieve a tissue regeneration effect, show stable and lasting pharmacological effects, even with a low concentration dose level of the peptides adhered thereto.

The examiner's attention is respectfully drawn to Test Examples 3 and 4 of the present application, at pages 20-22, where successful use of the claimed scaffold is illustrated.

Therefore one of skill in the art would not have attempted to use peptides in the range of the claimed concentration, as the prior art taught away from such low levels.

Based on the foregoing, White et al. in view of Knopf, Gauvreau et al. and Frankel et al. fails to provide any logical basis for the scaffold recited in claims 10, 13, 21 and 22. White et al. in view of Knopf, Gauvreau et al. and Frankel et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 10, 13, 21 and 22 under 35 U.S.C. § 103(a) as being obvious over White et al. in view of Knopf, Gauvreau et al. and Frankel et al. is respectfully requested.

Additionally, the examiner rejected claim 19 under 35 U.S.C. §103(a) as unpatentable over White et al. in view of Knopf, Gauvreau et al. and Frankel et al. and further in view of Puleo et

al., 2002, *Biomaterials* 23:2079-2087 (hereinafter Puleo et al.). Applicants respectfully traverse the rejection.

Claim 19 is of dependent form under claim 10 and is correspondingly distinguished over the combination of White et al. in view of Knopf, Gauvreau et al. and Frankel et al. The examiner further cites Puleo et al. as teaching a titanium implant useful as a surface of a scaffold of claim 10. However, Puleo et al. fails to remedy the deficiencies in the combination of White et al. in view of Knopf, Gauvreau et al. and Frankel et al., as discussed in detail above.

Therefore, White et al. in view of Knopf, Gauvreau et al., Frankel et al. and Puleo et al. fails to provide any logical basis for the scaffold recited in claim 19. White et al. in view of Knopf, Gauvreau et al., Frankel et al. and Puleo et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claim 19 under 35 U.S.C. § 103(a) as being obvious over White et al. in view of Knopf, Gauvreau et al., Frankel et al. and Puleo et al. is respectfully requested.

F. Fee Payable for Added Claim 23

By the present Amendment, 1 new independent claim has been introduced. Addition of this claim brings the total number of pending independent claims in this application to two and the total number of claims to ten. Accordingly, no fees are believed to be due in connection with addition of new claim 23.

CONCLUSION

Based on the foregoing, all of applicants' pending claims 10, 13, and 21-23 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the October 14, 2009 Office Action without extension was set at three months, or January 14, 2010. Applicants hereby request a three month extension of time under 37 CFR § 1.136 to extend the deadline for response to April 14, 2010. Payment of the extension fee of $555.00 specified in 37 C.F.R. §1.17(a)(3) and the RCE fee of $405.00 specified in 37 C.F.R. §1.17(e), as applicable to small entity, is being made by on-line credit card authorization at the time of EFS submission of this Response, for a total fee submission of $960.00. Should

any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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